CHEST

Characterization of Severe Asthma Worldwide

Data From the International Severe Asthma Registry

Eileen Wang, MD, MPH; Michael E. Wechsler, MD; Trung N. Tran, MD, PhD; Liam G. Heaney, MD; Rupert C. Jones, MD; Andrew N. Menzies-Gow, MD; John Busby, PhD; David J. Jackson, MD, PhD; Paul E. Pfeffer, MD, PhD; Chin Kook Rhee, MD, PhD; You Sook Cho, MD, PhD; G. Walter Canonica, MD; Enrico Heffler, MD, PhD; Peter G. Gibson, D Med; Mark Hew, PhD; Matthew Peters, MD, PhD; Erin S. Harvey, PhD; Marianna Alacqua, MD, PhD; James Zangrilli, MD; Lakmini Bulathsinhala, MPH; Victoria A. Carter, BSc; Isha Chaudhry, MSc; Neva Eleangovan, BSc; Naeimeh Hosseini, MD; Ruth B. Murray, PhD; and David B. Price, MD

BACKGROUND: Clinical characteristics of the international population with severe asthma are unknown. Intercountry comparisons are hindered by variable data collection within regional and national severe asthma registries. We aimed to describe demographic and clinical characteristics of patients treated in severe asthma services in the United States, Europe, and the Asia-Pacific region.

METHODS: The International Severe Asthma Registry retrospectively and prospectively collected data in patients with severe asthma (≥ 18 years old), receiving Global Initiative for Asthma (GINA) Step 5 treatment or with severe asthma remaining uncontrolled at GINA Step 4. Baseline demographic and clinical data were collected from the United States, United Kingdom, South Korea, Italy, and the Severe Asthma Web-based Database registry (including Australia, Singapore, and New Zealand) from December 2014 to December 2017.

RESULTS: We included 4,990 patients. Mean (SD) age was 55.0 (15.9) years, and mean (SD) age at asthma onset was 30.7 (17.7) years. Patients were predominantly female (59.3%) and white (72.6%), had never smoked (60.5%), and were overweight or obese (70.4%); 34.9% were at GINA Step 5; and 57.2% had poorly controlled disease. A total of 51.1% of patients were receiving regular intermittent oral corticosteroids, and 25.4% were receiving biologics (72.6% for those at GINA Step 5). Mean (SD) exacerbation rate was 1.7 (2.7) per year. Intercountry variation was observed in clinical characteristics, prescribed treatments, and biomarker profiles.

CONCLUSIONS: Using a common data set and definitions, this study describes severe asthma characteristics of a large patient cohort included in multiple severe asthma registries and identifies country differences. Whether these are related to underlying epidemiological factors, environmental factors, phenotypes, asthma management systems, treatment access, and/or cultural factors requires further study. CHEST 2020; 157(4):790-804

KEY WORDS: biologics; comorbidity; eosinophils; FENO; IgE

ABBREVIATIONS: ACO = asthma-COPD overlap; AR = allergic rhinitis; BEC = blood eosinophil count; CRS = chronic rhinosinusitis; FENO = fractional exhaled nitric oxide; GINA = Global Initiative for Asthma; HCRU = health-care resource use; ISAR = International Severe Asthma Registry; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; NP = nasal polyp; OCS = oral corticosteroid; ppb = parts per billion; SAWD = Severe Asthma Web-based Database; Th2 = helper T cell

AFFILIATIONS: From the Division of Allergy & Clinical Immunology (Dr Wang), Department of Medicine, National Jewish Health, Denver, CO, and Division of Allergy & Clinical Immunology,

Severe asthma is defined as "asthma which requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled,' or which remains 'uncontrolled' despite this therapy."[1] Other definitions include lack of control with use of maximal optimized therapy and treatment of contributory factors.[2] Severe asthma is thought to affect approximately 5% to 10% of the total population with asthma,[1] although a large prevalence range (1.8%-38%) has been reported.[3] Severe asthma is associated with significant morbidity[4] and mortality[5-7] and treatment,[8] psychological,[9] and socioeconomic[10] burdens, with much of the cost attributable to oral corticosteroid (OCS)-induced morbidity.[11,12] The cost per patient of severe asthma can be tenfold higher than that of mild disease, accounting for more than 60% of asthma-related health-care costs.[13] Many patients are unable to maintain full-time employment,[14] with a high degree of presenteeism and absenteeism reported.[15]

The World Health Organization emphasizes asthma's contribution to the global symptom and economic burden and calls for "better surveillance to map the magnitude of chronic respiratory diseases and analyze their determinants…and to monitor future trends."[16] The Global Asthma Report stresses the need for asthma monitoring to be ongoing, appealing for countries to conduct asthma surveillance, with regular investigation of trends.[17]

Regional and national severe asthma registries already exist and collect valuable country-specific data.[18-25] However, they typically contain relatively small numbers and tend to target specific subsets of severe asthma. Combining data is delayed until individual registry data are published and is hindered by different definitions used and variables collected. The International Severe Asthma Registry (ISAR; http://isaregistries.org/), the first worldwide adult severe asthma registry, overcomes some of these limitations[26,27] and answers the World Health Organization and Global Asthma Report calls to action.[16,17] In partnership with national and regional registries, ISAR collects patient-level, pseudonymous, longitudinal, real-life, standardized, high-quality data, using a set of core variables, from countries across the world for ethically approved research purposes.[27] ISAR contains data in a greater breadth of patients within the severe asthma definition and has sufficient power to answer important clinical questions. The aim of this article is to describe the demographic and clinical characteristics of patients with severe asthma treated in secondary and tertiary asthma centers in the United States, Europe, and the Asia-Pacific region and to study intercountry differences.

Materials and Methods

Patients

Because this is a historical, registry study, patients were not recruited but rather included into ISAR from other existing and newly created registries. ISAR essentially acts as a data custodian. Participating countries retain ownership of their own data but have agreed to provide access to, and share anonymous patient-level data with, ISAR for approved research purposes. Patient data are transferred to the ISAR database at regular intervals. Details of how data are extracted from national registries to ISAR are provided in the online

Department of Internal Medicine, University of Colorado Hospital, Aurora, CO; NJH Cohen Family Asthma Institute (Dr Wechsler), Department of Medicine, National Jewish Health, Denver, CO; AstraZeneca (Drs Tran and Zangrilli), Gaithersburg, MD; UK Severe Asthma Network and National Registry (Drs Heaney and Busby), Queen's University Belfast, Belfast, Northern Ireland; Faculty of Medicine and Dentistry (Dr Jones), University of Plymouth, Plymouth, United Kingdom; UK Severe Asthma Network and National Registry (Dr Menzies-Gow), Royal Brompton & Harefield NHS Foundation Trust, London, United Kingdom; UK Severe Asthma Network and National Registry (Dr Jackson), Guy's and St Thomas' NHS Trust and Division of Asthma, Allergy & Lung Biology, King's College London, London, United Kingdom; UK Severe Asthma Network (Dr Pfeffer), Barts Health NHS Trust and Queen Mary University of London, London, United Kingdom; Division of Pulmonary, Allergy and Critical Care Medicine (Dr Rhee), Department of Internal Medicine, St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea; Department of Internal Medicine (Dr Cho), Division of Allergy and Clinical Immunology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Personalized Medicine Asthma & Allergy Clinic (Drs Canonica and Heffler), Humanitas University & Research Hospital, Milan, Italy and SANI-Severe Asthma Network Italy, Italy; Australian Severe Asthma Network (Drs Gibson and Harvey), Priority Research Centre for Healthy Lungs, University of Newcastle, Newcastle, NSW, Australia; Hunter Medical Research Institute (Drs Gibson and Harvey), Department of Respiratory and Sleep Medicine, John Hunter Hospital, New Lambton Heights, NSW, Australia; Allergy, Asthma & Clinical Immunology Service (Dr Hew), Alfred Health, Melbourne, VIC, Australia; Public Health and Preventive Medicine (Dr Hew), Monash University, Melbourne, VIC, Australia; Department of Thoracic Medicine (Dr Peters), Concord Hospital, Sydney, NSW, Australia; AstraZeneca plc (Dr Alacqua), Cambridge, United Kingdom; Optimum Patient Care Global Ltd (Drs Bulathsinhala, Hosseini, Murray, and Price; and Mss Carter, Chaudhry, and Eleangovan), Cambridge, England; Observational and Pragmatic Research Institute (Dr Price), Singapore, Republic of Singapore; and Centre of Academic Primary Care (Dr Price), Division of Applied Health Sciences, University of Aberdeen, Aberdeen, United Kingdom.

FUNDING/SUPPORT: The International Severe Asthma Registry is conducted by Optimum Patient Care (OPC) Global Ltd and co-funded by AstraZeneca and OPC Global Limited.

CORRESPONDENCE TO: David B. Price, MD, Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth Bldg, Foresterhill, Aberdeen AB25 2ZD, Scotland; e-mail: dprice@opri.sg

DOI: https://doi.org/10.1016/j.chest.2019.10.053

supplement (e-Appendix 1). A country lead has been identified for each registry and is responsible for overseeing data collection, including combining data from any satellite sites, before making the countrywide data available to ISAR. This approach, in effect, allows for the creation of a locally hosted central registry for the country's combined data, which can be used to enhance local- and international-level research. Full details about asthma diagnostic criteria and the definition of severe asthma for each of these registries are provided in the online supplement (e-Tables 1, 2). Patients in ISAR are 18 years or older, received treatment at Global Initiative for Asthma (GINA) Step 5 or had uncontrolled asthma at GINA Step 4 (at inclusion),[1,28] and provided consent for their data to be included (except in the United States, where consent was not required because data were deidentified). Smokers and those with asthma-COPD overlap (ACO) were not excluded. ISAR is currently developing a protocol to identify patients with ACO within its severe asthma cohort. These eligibility criteria were chosen to reflect patients with severe asthma in the real-world setting and to broaden the scope to include patients with uncontrolled moderate to severe asthma.

Data Collected

Aggregated baseline demographic and clinical data for prespecified analyses were transferred to ISAR from secondary and tertiary severe asthma centers in the United Kingdom, Italy, South Korea, and Australia. Patient-level data were contributed by the United States. Patients in the US registry were identified by meeting the ISAR eligibility criteria on the basis of their diagnostic labeling medications to assess GINA Step 4 or Step 5 treatment and asthma control test score and/or prebronchodilator $FEV_1 < 80\%$ predicted to ascertain asthma control status from their retrospective electronic medical health records. Data were collected from the following registries from December 2014 to December 30, 2017: National Jewish Health Electronic Medical Record Severe Asthma Cohort (United States, from all regions [predominantly Colorado and Wyoming] and a small proportion from other countries); the UK Severe Asthma Network and National Registry (four sites)[19]; the Korean Academy of Asthma, Allergy and Clinical Immunology registry (15 sites)[25]; the Severe Asthma Network Italy (61 sites)[24]; and the Australasian Severe Asthma Network's registry (ie, Severe Asthma Web-based Database [SAWD], including patient data from Australia, Singapore, and New Zealand: 23 sites).[20]

ISAR captures 95 core variables agreed by means of Delphi consensus.[27] Those presented in this article are summarized in e-Tables 3 and 4. The number of exacerbations was defined as the number requiring rescue systemic corticosteroids in the past 12 months. The United States used duration of OCS as a proxy for exacerbation (assuming one OCS course lasts ≥ 7 days), in line with GINA 2018 recommendations and previously published research and based on discussion with the site investigator.[28,29] A retrospective analysis of National Jewish Health prescriptions showed that most prednisolone prescriptions were for at least 7 days for short-term use. The number of hospitalization and ED admissions for asthma was the number in the past 12 months. The number of times invasive ventilation was used was the number of episodes before data extraction. Comorbidity was based on a formal diagnosis or reliably inferred from relevant prescription data. For the United States, comorbidity data were captured using *International Classification of Diseases, Tenth Revision* codes for active diagnosis of comorbidity. Prescription data were used as a supplement to identify the comorbidity status of allergic rhinitis (AR) and eczema because their active diagnosis was underreported in the electronic medical records data. This finding was confirmed by the site lead (E. W.) and additional practitioners at the clinic. In addition to tracking regular OCS use (defined as ≥ 90 days of OCS use in a year), to capture risk for systemic corticosteroid adverse effects, intermittent OCS use was defined as the prescription for repeated OCS use and/or ≥ 2 exacerbations in a 1-year period.[30] Asthma control was categorized as controlled, partly controlled, or uncontrolled according to GINA criteria,[28] determined using the Asthma Control Test questionnaire[31] or the Asthma Control Questionnaire.[32]

Ethics and Governance

This study was designed, implemented, and reported in accordance with the European Network Centres for Pharmacoepidemiology and Pharmacovigilance (European Medicines Agency 2014; EUPAS25489; http://www.encepp.eu/encepp/viewResource.htm?id=27888) and performed in compliance with all applicable local and international laws and regulations. Governance was provided by the Anonymised Data Ethics Protocols and Transparency committee (protocol 2249). All registries participating in ISAR received ethical approval in their own countries and obtained regulatory agreement to provide deidentified data to ISAR in compliance with country-specific international data transfer laws and legislation and their relevant ethical boards and organizations. All patient-level data extracted and transferred from the United States were deidentified and entered into the research database as anonymized patient identification numbers.

Statistical Analysis

Data were assessed using Stata version 14 (StataCorp) or SAS version 9.4 or 9.5 (SAS Institute) according to a predefined data analysis plan to minimize bias. Descriptive statistics were reported as categorical variables for all variables for the overall and country-specific patient populations. Health-care resource use (HCRU), IgE count, blood eosinophil count (BEC), and comorbidities also were stratified by severe asthma status and sex for the overall population.

Results

Demographic Characteristics

The study included 4,990 eligible patients with individual-level data from the United States (n = 3,286) and aggregate data from the United Kingdom (n = 696), South Korea (n = 439), Italy (n = 310), and the SAWD registry (n = 259). Mean (SD) age was 55 (15.9) years, and mean (SD) age at asthma onset was 30.7 (17.7) years. Patients were predominantly female (59.3%), were aged 55 to 79 years (52.1%), were white (72.6%), had never smoked (60.5%), and were overweight or obese (70.4%); 34.9% were at GINA Step 5; and 57.2% had poorly controlled disease. A total of 51.1% of patients were receiving regular intermittent OCS, and 25.4% were receiving biologics (72.6% for those at GINA Step 5). Mean (SD) exacerbation rate was 1.7 (2.7) per year (Table 1). South Korea had the oldest patients, the lowest prevalence of patients who were overweight or obese, and the highest prevalence of current smokers (12.1%). Approximately one-third of individuals from the SAWD registry (30.0%), South Korea (33.9%), and the United States (36.8%) were exsmokers (e-Table 5).

TABLE 1] Demographic Characteristics of All Patients in the ISAR Database

Characteristic	Data
Sex, No. (%) (n = 4,986)	
Female	2,957 (59.3)
Male	2,029 (40.7)
Age, y (n = 4,967)	
Mean (SD)	55.0 (15.9)
18-34, No. (%)	658 (13.2)
35-54, No. (%)	1,510 (30.4)
55-79, No. (%)	2,588 (52.1)
≥ 80, No. (%)	211 (4.2)
Ethnicity, No. (%) (n = 4,912)	
White	3,568 (72.6)
Asian	589 (12.0)
African	263 (5.4)
Mixed	31 (0.6)
Other	130 (2.6)
Unknown	331 (6.7)
BMI, No. (%), kg/m^2 (n = 4,901)	
Underweight (< 18.5)	105 (2.1)
Normal (≥ 18.5 to < 25)	1,345 (27.4)
Overweight (≥ 25 to < 30)	1,531 (31.2)
Obese (≥ 30)	1,920 (39.2)
Smoking status, No. (%) (n = 4,947)	
Current smoker	294 (5.9)
Exsmoker	1,656 (33.5)
Never smoked	2,997 (60.6)

The number refers to the total number of patients with nonmissing data. Percentages may not total 100% because of rounding. ISAR = Internal Severe Asthma Registry.

Clinical Characteristics

Severity and Lung Function: Most patients had uncontrolled asthma at GINA Step 4 (Fig 1). There was a higher proportion of women both among patients with uncontrolled asthma at GINA Step 4 (59.3%) and among patients with asthma at GINA Step 5 (59.4%). Patients from the United Kingdom and Italy tended to have more severe disease, and those from the United States and South Korea tended to have the least severe compared with patients in other countries (Fig 1).

Percent predicted FEV_1 and FVC values appeared to be independent of severity, showed some intercountry variability, and showed little postbronchodilator improvement (Table 2). The mean (SD) postbronchodilator FEV_1/FVC was 0.69 (0.13) for patients at GINA Step 5 and 0.71 (0.13) for those with uncontrolled asthma at GINA Step 4 (Table 2), indicating a substantial presence of fixed airway obstruction. The percentages of patients with FEV_1/FVC < 0.7 were 43% and 47% for GINA Step 4 and Step 5, respectively. Bronchoconstriction was considered irreversible[33] for those in both severity groups and irrespective of smoking history. Some intercountry variability was noted (Table 3).[33,34] These findings not only justify the ISAR inclusion criteria for severe asthma but also ratify the definition of severe asthma as outlined by the European Respiratory Society and American Thoracic Society.[1] Incidentally, those with low or limited reversibility are routinely excluded from asthma clinical trials. The inclusive nature of ISAR and broad definition

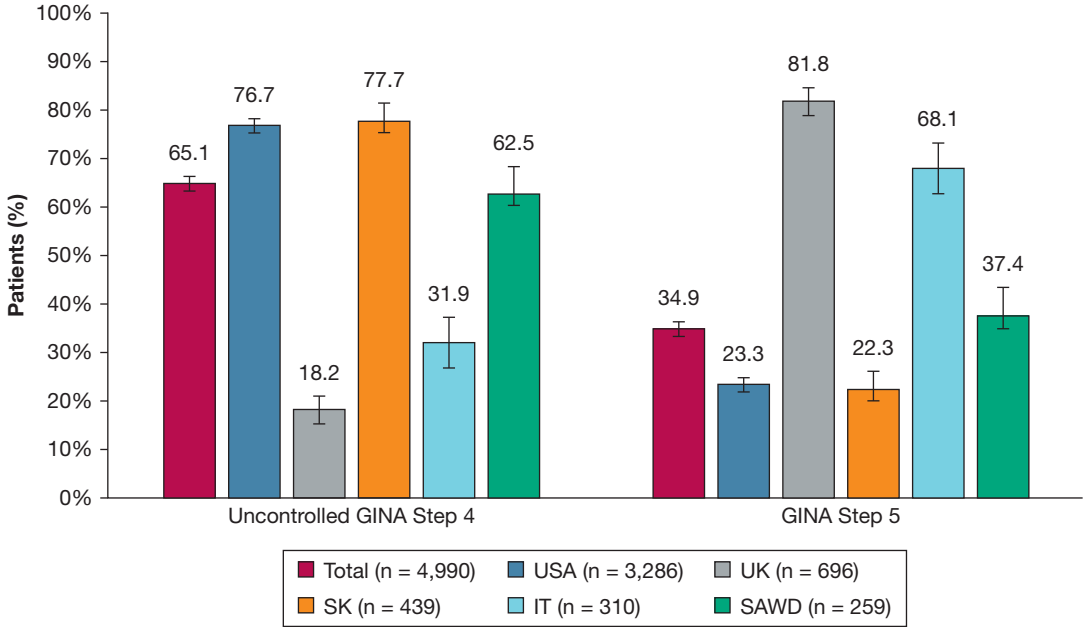

Figure 1 – *Asthma severity distribution in the total International Severe Asthma Registry population and by country. GINA = Global Initiative for Asthma; IT = Italy; SAWD = Severe Asthma Web-based Database; SK = South Korea; UK = United Kingdom; USA = United States.*

TABLE 2] Lung Function in Patients With Uncontrolled Asthma at GINA Step 4 or Asthma at GINA Step 5 Included in ISAR and According to Country and Registry

Country or Registry	Uncontrolled Asthma at GINA Step 4					
	Prebronchodilator			Postbronchodilator		
	FEV_1 (SD)	FVC (SD)	FEV_1/FVC (SD)	FEV_1 (SD)	FVC (SD)	FEV_1/FVC (SD)
All	71.9 (15.3) (n = 2,801)[a]	78.7 (14.9) (n = 2,936)	0.69 (0.12) (n = 2,633)	75.6 (16.0) (n = 2,104)	81.8 (14.6) (n = 2,501)	0.71 (0.13) (n = 1,755)
United States	72.3 (13.7) (n = 2,244)	78.2 (14.1) (n = 2,382)	0.70 (0.11) (n = 2,512)	75.8 (14.1) (n = 1,591)	81.4 (13.6) (n = 1,639)	0.71 (0.13) (n = 1,732)
United Kingdom	72.5 (22.3) (n = 117)	85.2 (17.8) (n = 114)	…[b]	77.5 (22.5) (n = 73)	91.5 (18.1) (n = 71)	…[b]
South Korea	68.1 (20.1) (n = 341)	76.7 (18.0) (n = 341)	0.6 (0.16) (n = 12)	73.8 (21.1) (n = 341)	81.9 (18.2) (n = 341)	0.62 (0.17) (n = 12)
Italy	74.2 (20.5) (n = 99)	91.5 (18.8) (n = 99)	0.65 (0.11) (n = 109)	77.1 (19.1) (n = 99)	…[c]	0.59 (0.14) (n = 11)
	GINA Step 5					
All	70.4 (19.0) (n = 1,437)[a]	82.5 (17.3) (n = 1,484)	0.68 (0.12) (n = 1,045)	76.2 (19.2) (n = 975)	84.5 (17.3) (n = 775)	0.69 (0.13) (n = 530)
United States	74.9 (15.8) (n = 625)	80.1 (15.3) (n = 688)	0.69 (0.11) (n = 740)	75.5 (15.6) (n = 390)	82.1 (14.2) (n = 413)	0.69 (0.13) (n = 445)
United Kingdom	65.2 (22.0) (n = 503)	84.5 (20.4) (n = 487)	…[b]	71.1 (21.9) (n = 276)	89.9 (20.5) (n = 264)	…[b]
South Korea	68.0 (20.7) (n = 98)	77.5 (19.0) (n = 98)	0.60 (0.13) (n = 8)	72.1 (21.4) (n = 98)	80.4 (19.8) (n = 98)	0.63 (0.15) (n = 8)
Italy	70.7 (18.8) (n = 211)	88.3 (18.4) (n = 211)	0.66 (0.13) (n = 297)	86.0 (20.5) (n = 211)	…[c]	0.68 (0.14) (n = 77)

FEV_1 and FVC data are presented as mean (SD) % predicted. The % predicted data are based on aggregate-level data from the United Kingdom, United States, South Korea, and Italy; aggregate data for % predicted lung function were not available for patients in the SAWD registry. FEV_1/FVC is derived from patient-level lung function data from the United States, South Korea, and Italy. GINA = Global Initiative for Asthma. See Table 1 legend for expansion of other abbreviation.
[a]The number refers to the total number of patients with nonmissing data.
[b]Patient-level data were used to compute the FEV_1/FVC ratio; these data were not available for the United Kingdom but were available for 12 and eight patients (GINA Steps 4 and 5, respectively) from South Korea.
[c]Data were not available for postbronchodilator % predicted FVC for Italy.

TABLE 3] Bronchodilator Reversibility (%) as a Function of Asthma Severity and Smoking Status for All Patients Included in ISAR and According to Country and Registry

Country	Uncontrolled at GINA Step 4		GINA Step 5	
	Smokers	Nonsmokers	Smokers	Nonsmokers
ERS definition (change from % predicted FEV_1, threshold > 9%)[33]				
All (n = 2,120)[a]	6.9% (6.9)	6.7% (7.8)	7.6% (8.1)	7.0% (8.6)
United States (n = 1,849)	7.0% (6.9)	6.6% (6.9)	7.0% (7.9)	6.5% (7.8)
South Korea (n = 20)	6.2% (6.9)	5.0% (4.9)	4.1% (3.1)	9.0% (5.1)
Italy (n = 251)	7.5% (7.0)	9.0% (17.5)	9.9% (9.0)	7.6% (9.8)
ATS definition (change from initial FEV_1 (%), threshold > 12%)[34]				
All (n = 2,238)[a]	12.0% (16.3)	8.2% (8.0)	13.2% (14.8)	12.0% (17.7)
United States (n = 1,967)	12.0% (16.4)	11.9% (17.9)	13.0% (15.4)	11.9% (17.4)
South Korea (n = 20)	10.1% (11.4)	13.1% (22.6)	6.9% (5.7)	11.4% (7.0)
Italy (n = 251)	10.7% (9.2)	13.1% (22.6)	14.8% (13.2)	12.1% (18.3)

Bronchodilator reversibility (% change in lung function) data are presented as mean (SD) bronchodilator reversibility according to ERS and ATS definitions. ATS = American Thoracic Society; ERS = European Respiratory Society. See Tables 1 and 2 legends for expansion of other abbreviations.
[a]The number represents the total number of patients with nonmissing data and includes patients at both GINA Step 4 and GINA Step 5. Patient-level data from the United States and Italy were used to compute bronchodilator reversibility (% change in lung function); these data were not available for the United Kingdom but were available for 20 patients from South Korea.

TABLE 4] Demographic and Clinical Characteristics for All Patients Included in ISAR and According to Country and Registry

	Patients With Uncontrolled Asthma at GINA Step 4 or at GINA Step 5							Patients at GINA Step 5 Only[a]	
Country or Registry	Age, Mean (SD), y	Overweight or obese, % (95% CI)	Age at Onset, Mean (SD), y	Exacerbations per Year, Mean (SD)	Receiving Repeated Intermittent OCS, % (95% CI)	Receiving Regular OCS, % (95% CI)	Receiving Biologics (Anti-IgE or Anti-IL-5), % (95% CI)	Receiving Regular OCS, % (95% CI)	Receiving Biologics (Anti-IgE or Anti-IL-5), % (95% CI)
All (N = 4,990)	55.0 (15.9)	70.4 (69.1-71.7)	30.7 (17.7)	1.7 (2.7)	51.1 (49.8-52.5)	30.1 (24.5-35.7)	25.4 (24.2-26.6)	48.8 (38.8-58.7)	72.6 (63.8-81.5)
United States (n = 3,286)	55.5 (16.7)	74.2 (70.0-78.3)	…[b]	0.8 (1.6)[c]	26.8 (25.3-28.4)	23.3 (21.8-24.7)	16.2 (15.0-17.5)	20.4 (17.5-23.2)	69.8 (60.7-78.9)
United Kingdom (n = 696)	48.3 (14.1)	78.2 (74.3-82.1)	25.4 (18.7)	5.0 (4.0)	100.0 (0-0)	59.6 (56.0-63.3)	67.3 (63.8-70.8)	72.9 (69.3-76.6)	82.4 (74.8-89.9)
South Korea (n = 439)	62.4 (14.1)	35.1 (30.6-39.6)	41.0 (17.1)	1.1 (1.5)	48.3 (43.6-53.0)	20.7 (16.9-24.5)	1.4 (0.3-2.4)	92.9 (87.8-98.0)	6.1 (1.4-10.9)
Italy (n = 310)	54.5 (13.8)	54.6 (49.9-59.3)	34.4 (17.1)	3.7 (7.2)	92.3 (89.3-95.2)	63.1 (56.5-69.1)	69.3 (64.2-74.5)	61.4 (54.9-68.0)	100.0 (0-0)
SAWD (n = 259)[d]	55.1 (15.3)	80.6 (76.9-84.3)	22.7 (17.1)	3.3 (2.9)	85.3 (81.0-89.6)	24.7 (19.5-30.0)	17.0 (12.4-21.6)	66 (56.6-75.4)	45.4 (35.5-55.2)

Exacerbations are defined as requiring rescue steroids in the past year or are defined according to OCS duration (assuming one course lasts ≥ 7 days). Regular OCS is defined as a prescription for ≥ 90 days of OCS exposure in the observation year. Intermittent OCS use is defined as a prescription for repeated OCS use and/or ≥ 2 exacerbations (treated with OCS). OCS = oral corticosteroid; SAWD = Severe Asthma Web-based Database. See Tables 1 and 2 legends for expansion of other abbreviations.

[a]GINA Step 5: All (n = 1,740), United States (n = 765), United Kingdom (n = 569), South Korea (n = 98), Italy (n = 211), SAWD (n = 97).

[b]US data were not available for age at asthma onset.

[c]The duration of OCS exposure was used as a proxy for asthma exacerbation assuming one course lasts ≥ 7 days.

[d]Australia (n = 225), Singapore (n = 16), and New Zealand (n = 18).

of severe asthma means that for the first time this population can be properly studied and characterized.

Age at Onset: The mean (SD) age at onset was 30.7 (17.7) years; 77.5% of patients developed asthma after the age of 12 years and 34.4% developed it after the age of 40 years. Patients from the United Kingdom and the SAWD registry developed asthma slightly earlier than this, and those from South Korea and Italy slightly later (Table 4, e-Table 6).

Asthma Control, Exacerbations, and HCRU: Figure 2 shows the proportion of patients with well-controlled, poorly controlled, and uncontrolled asthma[31,32] in the total population and also in each of the individual registries. At entry to their national registry, 57.2% of patients had poorly controlled asthma; this percentage was highest in the United Kingdom and the SAWD registry and lowest in Italy and South Korea. The proportions of patients with well-controlled, partly controlled, and uncontrolled asthma were similar in the GINA Step 4 (uncontrolled asthma at entry) and GINA Step 5 groups (e-Fig 1). The mean (SD) number of exacerbations (past 12 months) was 1.7 (2.7). One-quarter of patients reported ≥ 4 exacerbations (Fig 3). The number of exacerbations was driven by severity, with most patients with uncontrolled asthma at GINA Step 4 (at inclusion) reporting 0 exacerbations (71.1%), whereas 42.5% of patients at GINA Step 5 reported ≥ 4 exacerbations. The mean number of exacerbations was lowest in the United States and South Korea and highest in the United Kingdom (Fig 3, Table 4). HCRU was high overall but highest in the United Kingdom and lowest in South Korea (Fig 4), and was slightly higher for patients at GINA Step 5 (e-Fig 2, e-Table 6).

IgE Concentration: One-half of the patient population with severe asthma had low IgE concentrations (< 150 IU/mL) (Fig 5A). The IgE profile varied according to severity. More patients with uncontrolled asthma at GINA Step 4 (vs GINA Step 5) had low IgE concentrations (59.4% vs 43.7%). Conversely, more patients at GINA Step 5 (vs those with uncontrolled asthma at GINA Step 4) had high IgE concentrations (30.6% vs 23.3%). More women had low IgE concentrations, and more men had high IgE concentrations, irrespective of severity. Most patients from the United States had low IgE serum concentrations, whereas patients from the United Kingdom, South Korea, and the SAWD registry showed a more even split between low vs intermediate or high IgE concentrations. An even distribution of patients across the IgE concentration categories was noted in Italy (Fig 5A).

BEC: For BEC, 48.5% of patients had a BEC > 0.3 $\times 10^9$/L. Most patients in the United States, South Korea, and the SAWD registry had a BEC ≤ 0.3 $\times 10^9$/L, whereas most patients from the United Kingdom and Italy had a BEC > 0.3 $\times 10^9$/L (Fig 5B).

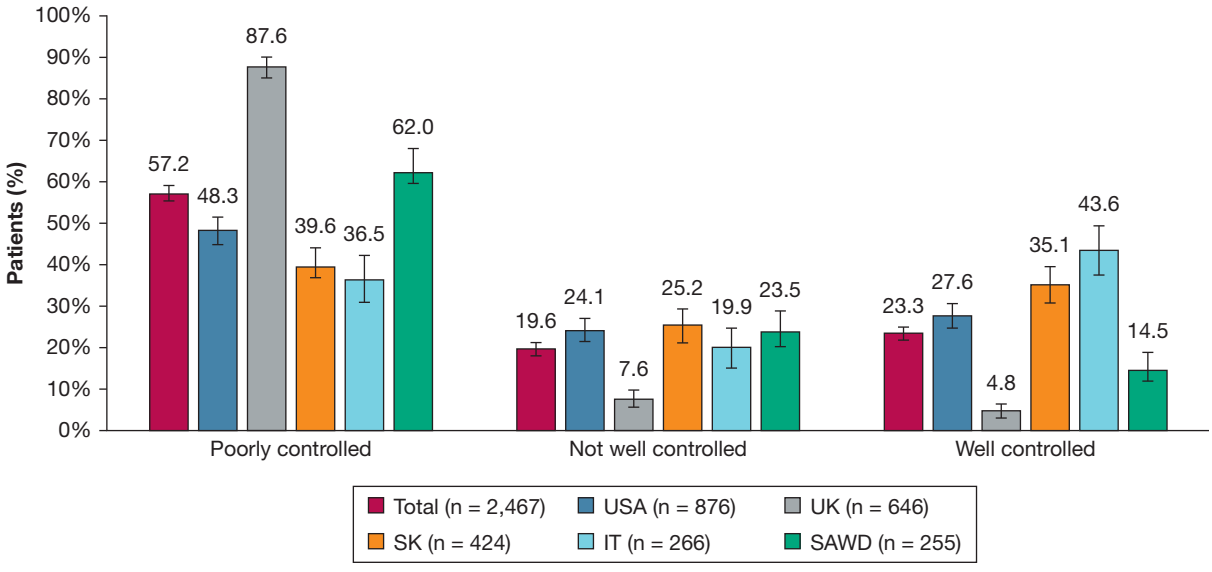

Figure 2 – *Proportion of patients with poorly controlled, not well-controlled, and well-controlled asthma in the total International Severe Asthma Registry population and by country. Control is defined according to Asthma Control Test or Asthma Control Questionnaire categorizations. Asthma Control Test: well controlled, 20 to 25; not well controlled, 16 to 20; and very poorly controlled, 5 to 15.*[31] *Asthma Control Questionnaire: well controlled, 0 to 0.75; gray zone, 0.75 to 1.5; and poorly controlled, > 1.5.*[32] *See Figure 1 legend for expansion of abbreviations.*

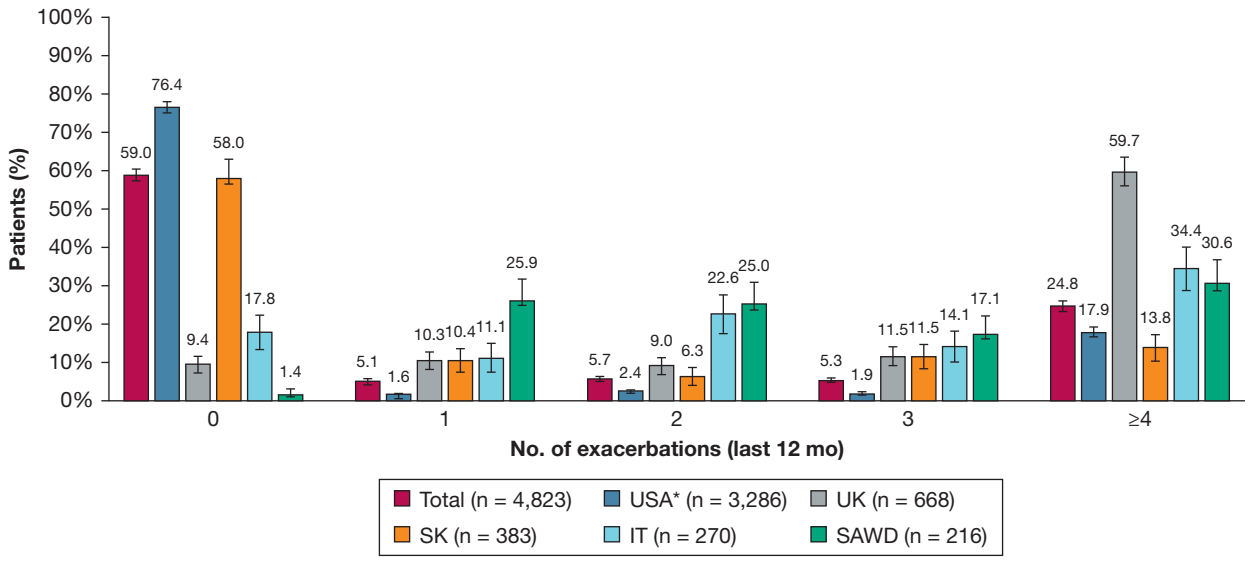

Figure 3 – *Proportion of patients with 0, 1, 2, 3, and ≥ 4 asthma exacerbations in the past 12 months in the total International Severe Asthma Registry population and by country. An exacerbation was defined as a symptom episode requiring rescue steroids in the past year. *In the United States, duration of oral corticosteroid (OCS) was used as a proxy for exacerbation (assuming one OCS course lasts ≥ 7 days). See Figure 1 legend for expansion of other abbreviations.*

Fractional Exhaled Nitric Oxide: Overall, 43.1% of patients with severe asthma had fractional exhaled nitric oxide (FENO) concentrations < 25 parts per billion (ppb), and 56.9% had a concentration ≥ 25 ppb. In the United States, a similar proportion of patients had FENO concentrations < 25 ppb and ≥ 25 ppb. Most patients from the United Kingdom, South Korea, and Italy had FENO concentrations ≥ 25 ppb, whereas most patients in the SAWD registry had FENO concentrations < 25 ppb (Fig 5C).

Comorbidities: AR was the predominant comorbidity (49.4%) in the total population, followed by chronic rhinosinusitis (CRS; 21.4%), eczema (9.6%), and nasal polyps (NPs; 7.3%). AR was the predominant comorbidity in all countries. The United States had the highest prevalence of comorbid CRS (26.8%), the SAWD registry had the highest eczema prevalence (20.5%), and Italy had the highest NP prevalence (22.3%) (e-Fig 3, e-Table 6).

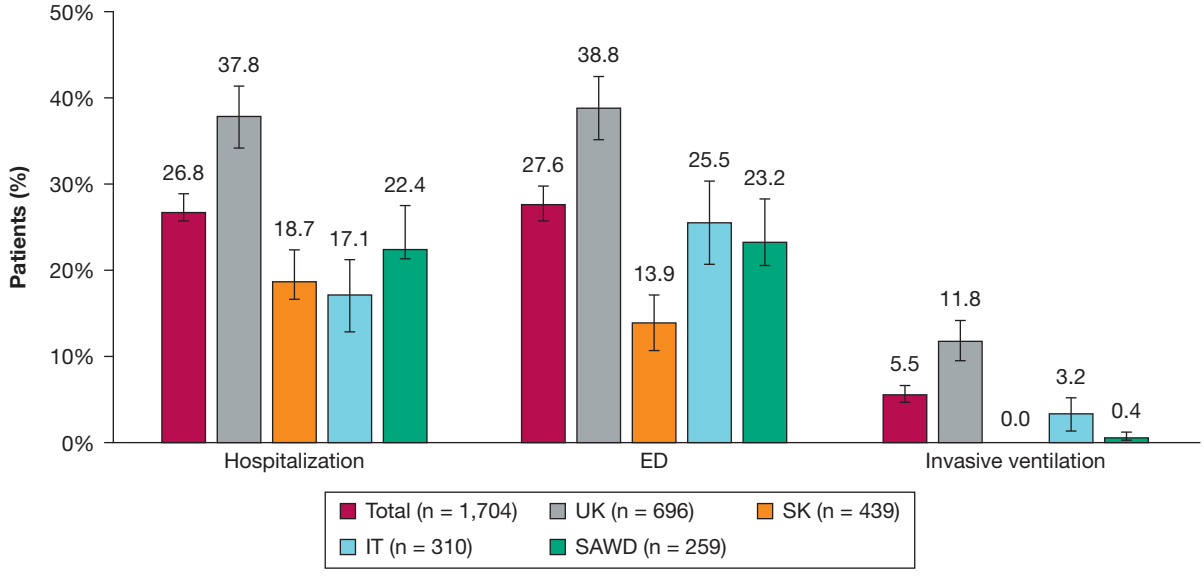

Figure 4 – *Health-care resource use (HCRU) in the total International Severe Asthma Registry population and by country. HCRU data were not available for the United States. See Figure 1 legend for expansion of other abbreviations.*

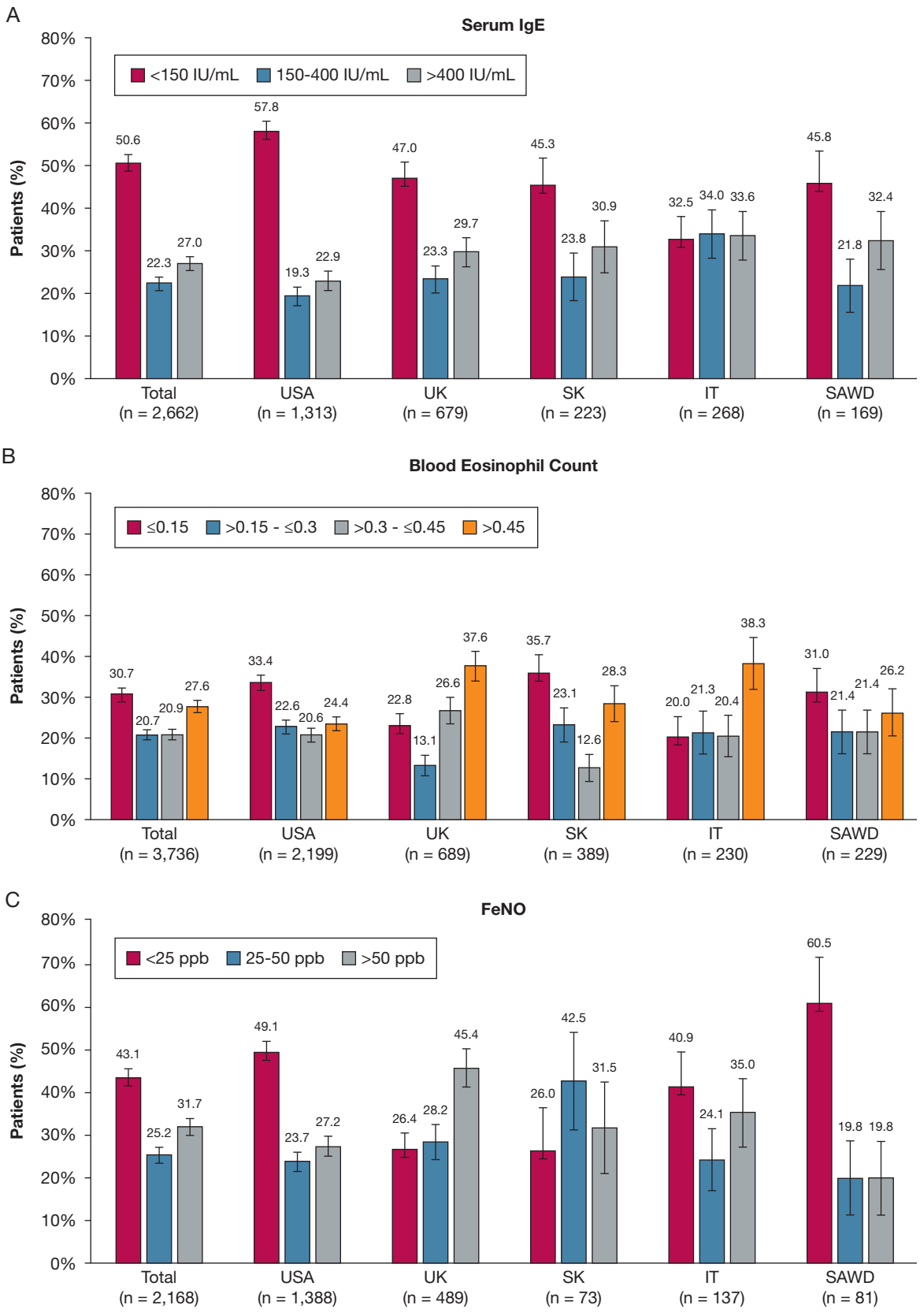

Figure 5 – *Biomarker distribution in the total International Severe Asthma Registry population and across countries. A, Serum IgE. B, Blood eosinophil count (×10⁹/L). C, Fractional exhaled nitric oxide (FENO). See Figure 1 legend for expansion of other abbreviations.*

Treatment: Across all patients (ie, those at GINA Step 4 or Step 5), 51.1% were receiving repeated intermittent OCS. Those from the United Kingdom, Italy, and the SAWD registry had the highest intermittent OCS use, and the United States had the lowest (Table 4).

All patients with uncontrolled asthma at GINA Step 4 were receiving inhaled corticosteroid and long-acting β_2-agonist therapy. The most common add-on to inhaled corticosteroid and long-acting β_2-agonist was leukotriene receptor antagonist (LTRA), followed by long-acting muscarinic receptor antagonist (LAMA) and theophylline (Fig 6A). The same pattern was noted in the US and UK registries. However, in South Korea, theophylline was used more commonly than was LAMA; in Italy, LAMA was used more commonly than was LTRA. The United Kingdom had the highest proportion of patients receiving add-on LAMA. Add-on therapy was used sparingly in the United States for patients with uncontrolled asthma at GINA Step 4 (at baseline) (Fig 6A).

Add-on regular OCS was used by almost one-half of the patients at GINA Step 5, anti-IgE and anti-IL-5 were each used by approximately one-third of patients,

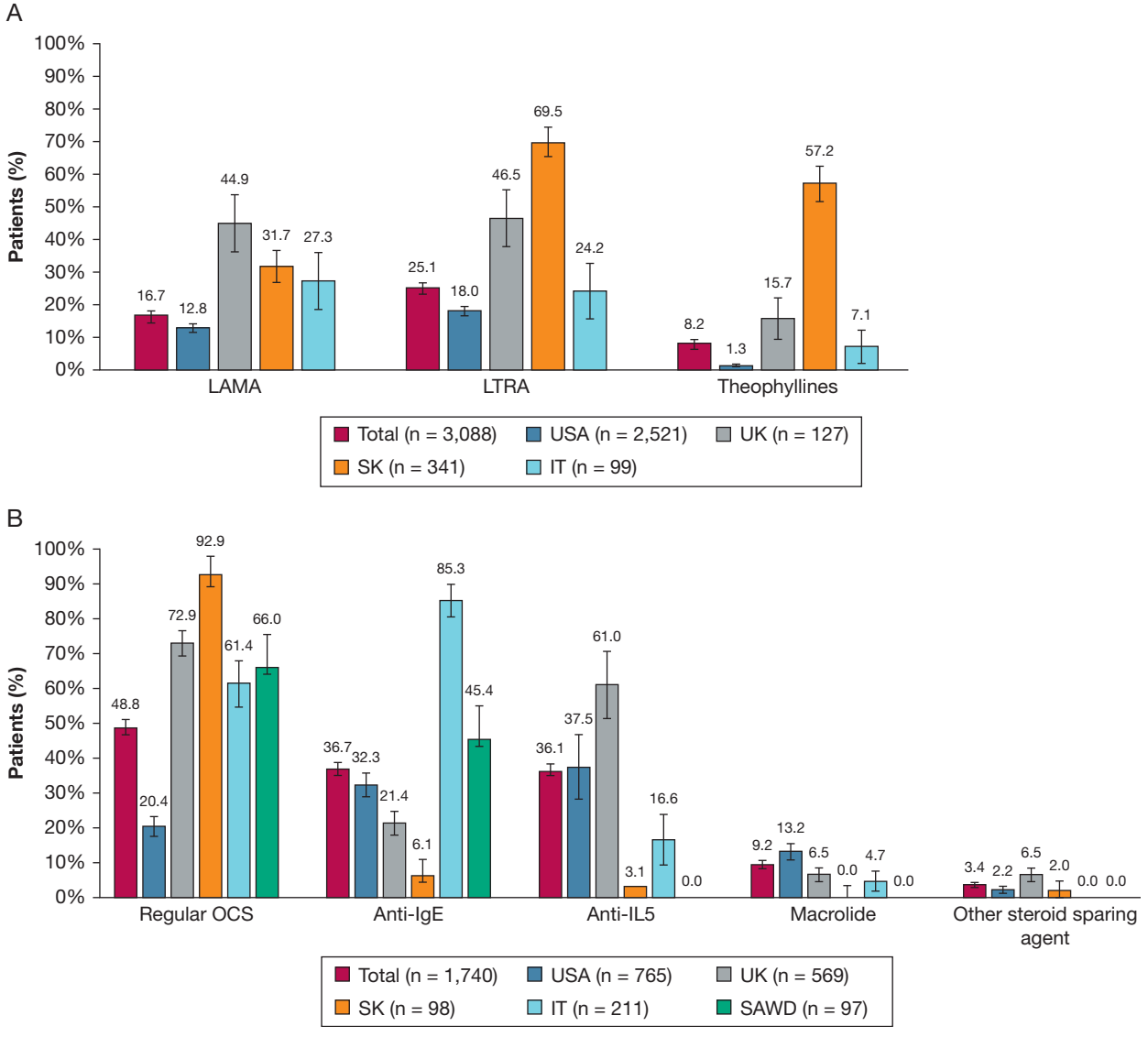

Figure 6 – *Medication regimen for (A) those with uncontrolled asthma at GINA Step 4 who were receiving inhaled corticosteroid and long-acting β_2-agonist add-on therapies and (B) those at GINA Step 5 in the total International Severe Asthma Registry population and by country. LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic receptor antagonist; LTRA = leukotriene receptor antagonist; SAWD data were not available for LAMA, LTRA (GINA Step 4), or anti-IL-5, macrolides, or other steroid-sparing agents (GINA Step 5). See Figures 1 and 3 legends for expansion of other abbreviations.*

and macrolides were prescribed for a minority. A wide range of intercountry variability was noted for regular OCS use (Fig 6B). Overall, 72.6% of patients with severe asthma at GINA Step 5 were receiving therapeutic monoclonal antibody therapy (ie, biologics), with notably high rates in Italy and the United Kingdom and a relatively low rate of use in South Korea (Fig 6B, Table 4). In Italy, the predominant biologic was anti-IgE, but in the United Kingdom it was anti-IL-5. The United States differed from other countries in having a fairly even split between anti-IgE and anti-IL-5 and also the highest proportion of patients receiving macrolides (Fig 6B).

Discussion

The international population with severe asthma is predominantly female, overweight or obese, nonsmoking, and in the 55- to 79-year age range. These patients experience 1.7 exacerbations per year on average, have poorly or not well-controlled asthma in the majority of cases, a low FEV_1/FVC ratio, limited reversibility, and high HCRU. AR is the predominant comorbid disease. There is a fairly even proportion of patients with a low vs an intermediate or high serum IgE concentration and BEC. Most patients have a high F_{ENO} concentration. Asthma treatment is severity specific. Approximately 30% of patients are receiving regular OCS therapy, more than 50% are receiving OCS intermittently, and approximately three-quarters of patients with most severe disease are receiving biologics.

There is substantial interregistry heterogeneity in the clinical characteristics of patients treated within severe asthma services. More work is required to explain many of these intercountry differences definitively. We hypothesize that some of these differences may be indicative of variations in cultural and epidemiological patterns, as well as environmental pressures. Other differences could reflect country-specific system issues (eg, differences in patient journey to severe asthma centers, selection bias, treatment landscape). Some differences may be explained by intrinsic differences in the asthma phenotype. ISAR has prioritized numerous research projects to help answer these outstanding questions such as investigating the effect of race, ethnicity, and socioeconomic status on asthma outcomes, assessing variability in biologic access and use (both within and between countries), and comparing OCS use patterns around the world (http://isaregistries.org/isar-research-updates/).

South Korea had the oldest patients, likely the result of its aging population,[35] and it has yet to experience the asthma epidemic seen in many Western countries in the past decades.[36] It has also the lowest prevalence of patients who were overweight or obese, perhaps because of the beneficial effect of South Korean traditional diets.[37] The high prevalence of current smokers in South Korea is in keeping with this older population, who often have ACO,[38] and is supported further by the generally poorer lung function and less reversibility noted for these patients. The relatively late onset of asthma in South Korea may be linked to recent economic development there, and the subsequent spike in air pollution, associated with an increase in hospital admissions for asthma.[39] Conversely, the relatively early age of onset of asthma in the United Kingdom and the SAWD registry may be a consequence of the epidemic of childhood asthma first described in the second one-half of the 20th century.[40] Age of onset could have implications for response to biologic therapy; patients with adult onset tend to respond better to anti-IL-5 or anti-IL-5 receptor, and those with younger onset tend to respond better to anti-IgE.[2,41]

Other intercountry differences noted could be the result of broad system differences. High numbers of patients at GINA Step 5 in the United Kingdom and Italy may occur because patients come from tertiary asthma centers (with strict referral criteria), so they naturally have the most severe disease. The high numbers with well-controlled asthma in Italy and the low numbers in the United Kingdom and the SAWD registry most likely are because in Italy patients are generally follow-up patients receiving biologic therapy, whereas those from the United Kingdom and the SAWD registry are generally patients at their first visit, before biologic use. These factors also help to explain the high exacerbation rate and HCRU in the United Kingdom, coupled with the fact that at least four exacerbations per year is required for biologic prescription in the United Kingdom.[42,43] In contrast, the high proportion of patients with well-controlled asthma in South Korea most likely reflects the rapid access to specialist care, which, along with the low cost of medications, may explain the low HCRU there.

The low exacerbation rate noted in the United States is most likely artificial because exacerbation data were not captured directly but rather by proxy and conservatively via OCS use. This is because exacerbations are rarely

coded in the US registry but rather added in the free-text box. Future work to capture this free-text information, as well as comorbidity information, is ongoing and will be provided in future analyses. In the interim, these data provide a useful benchmark to assess whether proxy OCS is a good or bad indicator of exacerbation rate. Definition overlap may account for the high prevalence of CRS (vs AR) in the United States, whereas routine nasal examination of patients in Italy may explain the high prevalence of NPs noted there. The high prevalence of eczema in the SAWD registry may be accounted for by a selection bias toward atopy, a requirement for omalizumab therapy.

Intercountry differences in treatment strategies also were noted. The high OCS and biologic use in both the United Kingdom and Italy may be severity driven. Biologic treatment patterns also differed among these countries, with Italy having high use of anti-IgE, the United Kingdom having high use of anti-IL-5, and the United States exhibiting an even split between anti-IgE and anti-IL-5. These different patterns probably reflect biologic availability or perhaps point to phenotypic differences. The high prevalence of LAMA and LTRA add-on therapy noted in the United Kingdom aligns with British Thoracic Society guideline-directed care for GINA Step 4[44] and is in keeping with treatment at primary care. In South Korea, high regular OCS use (for GINA Step 5) and add-on theophylline and LTRA use (for GINA Step 4) also were noted, but here the drivers may be different (eg, patient preference for oral therapies,[45] availability and reimbursement for these medications). Biologics are not reimbursed in South Korea and rarely used.

This first ISAR data set also facilitates categorization and comparison of asthma biomarker phenotypes across countries. The United Kingdom and Italy appear to have a predominance of helper T cell (Th2)-high, eosinophilic asthma, evidenced by high FENO and BEC.[2,46,47] The earlier onset of asthma in the United Kingdom, could indicate a predominance of allergic asthma, whereas the later asthma onset, and high prevalence of NPs in Italy suggest the predominance of a nonallergic phenotype.[48] Although baseline IgE levels may not predict the likelihood of response to biologics,[49] the higher BEC noted in both the United Kingdom and Italy predict a better response, both to anti-IgE[50,51] and to anti-IL-5 and anti-IL-5 receptor.[52] High exacerbation rates per year noted in both countries and the presence of NPs in Italy are also factors that may predict a good response to anti-IL-5 therapy.[2] In contrast, the lower BEC and low FENO biomarker profile noted for the SAWD registry is more indicative of a population predominantly with noneosinophilic, Th2-low asthma, whereas the profiles observed in the United States and South Korea registries are more ambiguous and could suggest a split of Th2-high and Th2-low asthma phenotypes (e-Table 6).

Merging data from preexisting registries brought its own challenges, including intercountry variability in the type of patients included in registries and standardization of variable definitions, as well as use of retrospective data. Although there was a bias toward white patients in this first ISAR data set, a much broader ethnic diversity will be contained in future data sets as ISAR continues to expand into Asia, Africa, and South America. A strength of this study is its size and the fact that data collected in registries are more heterogeneous than those collected in randomized controlled trials and are more representative of patients in real life.[53] Use of patient-level data also provides the opportunity to conduct biostatistical multivariate analyses, track patient progress longitudinally, and analyze response to treatment and changes in medical management. It is important to have both baseline and prospective data to describe the patient journey, to compare a baseline to a postbiologic timeline, and even to answer the question of who develops severe asthma.

Conclusions

This study provides the first description, to our knowledge, of an international population with managed severe asthma, and identified differences in demographic and clinical characteristics across country and health-care systems. Initial country-specific biomarker profiles have been identified. Whether inter-counter differences are related to underlying epidemiological factors, environmental factors, phenotypes, asthma management systems, treatment access, and/or cultural factors requires further study. Prospective data collection for the ISAR registry began in 2018 in Italy, the United States, South Korea, and the United Kingdom. Prospective data collection will ensure better standardization of data fields, facilitating more accurate cross-country comparisons and reducing any data incongruence in upcoming ISAR data sets.

Acknowledgments

Author contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors were involved in data acquisition, analysis or interpretation of data, as well as the critical revision of the manuscript for important intellectual content. Development of study concept and design was undertaken by T. N. T., L. B., and D. B. P.; E. W., R. B. M., and D. B. P. were responsible for drafting the manuscript. L. B., V. A. C., I. C., N. E., and N. H. provided additional administrative, technical, and material support. The study was supervised by D. B. P.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following: E. W. has received advisory board fees from AstraZeneca. She has been an investigator on clinical trials sponsored by GlaxoSmithKline, Teva, AstraZeneca, Novartis, National Institute of Allergy and Infectious Diseases (NIAID) for which her institution has received funding. She has received funding for investigator-initiated studies from Self Care Catalysts, Genentech, and GlaxoSmithKline. M. E. W. has received consulting honoraria from AstraZeneca plc, Boehringer Ingelheim, Genentech Inc, GlaxoSmithKline plc, Novartis International AG, Regeneron Pharmaceuticals Inc, Sanofi SA, Teva Pharmaceutical Industries Ltd and Equillium. T. N. T., M. A., and J. Z. are employees of AstraZeneca plc, a cofunder of the International Severe Asthma Registry. L. G. H. is Academic Lead for the UK MRC Consortium for Stratified Medicine in Severe Asthma - Industrial Pharma partners Amgen, AstraZeneca, Medimmune, Janssen, Novartis, Roche / Genentech, GlaxoSmithKline, and Boehringer Ingelheim; prior project grant funding from Medimmune, Novartis UK, Roche / Genentech, and GlaxoSmithKline; has taken part in Advisory Boards / Lectures supported by Novartis,Roche / Evelo Biosciences, Genentech, GlaxoSmithKline, Teva, Theravance and Vectura; has travel funding support to international respiratory meetings (AstraZeneca, Chiesi, Novartis, Boehringer Ingelheim, Teva, and GlaxoSmithKline) and has taken part in asthma clinical trials (GlaxoSmithKline, Schering Plough, Synairgen, Novartis, and Roche / Genentech) for which his institution was remunerated. R. C. J. declares grants from AstraZeneca, GlaxoSmithKline, and Novartis; and personal fees for consultancy, speakers fees, or travel support from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Nutricia, Observational & Pragmatic Research Institute, and Pfizer. A. N. M. G. declares grants from AstraZeneca plc, Boehringer Ingelheim, GlaxoSmithKline plc, and Hoffmann La Roche AG; consultancy agreements with AstraZeneca plc, Sanofi SA, and Vectura Group plc; attendance at advisory boards for AstraZeneca plc, Boehringer Ingelheim, GlaxoSmithKline plc, Novartis International AG, Sanofi SA, and Teva Pharmaceutical Industries Ltd; speaker fees from AstraZeneca plc, Boehringer Ingelheim, Novartis International AG, Teva Pharmaceutical Industries Ltd, and Vectura Group plc; and attendance at international conferences for Boehringer Ingelheim and Teva Pharmaceutical Industries Ltd. D. J. J. has received advisory board and speaker fees from AstraZeneca plc, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline plc, Napp Pharmaceuticals Limited, Novartis International AG, and Teva Pharmaceutical Industries Ltd and research grant funding from AstraZeneca plc. P. E. P. has attended advisory boards for Novartis International AG; has given lectures at meetings supported by AstraZeneca plc and GlaxoSmithKline plc; and has taken part in clinical trials sponsored by AstraZeneca plc, GlaxoSmithKline plc, and Novartis International AG, for which his institution received remuneration. C. K. R. declares consultancy and lecture fees from AstraZeneca plc, Boehringer Ingelheim, GlaxoSmithKline plc, Merck Sharp & Dohme Ltd, Mundipharma International Limited, Novartis International AG, Sandoz, Takeda Pharmaceutical Company Limited, and Teva-Handok Pharma Co Ltd. G. W. C. has received research grants and lecture or advisory board fees from A. Menarini Diagnostics Ltd, Allergy Therapeutics PLC, ALK-Abelló A/S, Anallergo SpA, AstraZeneca plc, Boehringer Ingelheim, Chiesi Farmaceutici, Circassia Pharmaceuticals, Danone SA, Faes Farma, Genentech Inc, Genzyme/Regeneron, GlaxoSmithKline plc, HAL Allergy Group, Laboratori Guidotti spa, Malesci Istituto Farmacobiologico spa, MedImmune LLC, Merck & Co Inc, Merck Sharp & Dohme Ltd, Mundipharma International Limited, Novartis International AG, Orion Pharma Ltd, Sanofi SA, Stallergenes Greer Ltd, Teva Pharmaceutical Industries Ltd, Thermo Fisher Scientific, UCB Pharmaceuticals, Uriach Group, and Valeas SpA. E. H. participates in speaking activities and industry advisory committees for AstraZeneca, Sanofi-Genzyme, GSK, Novartis, TEVA, Circassia and Nestlè Purina. P. G. G. declares speaker fees and grants to his institution from AstraZeneca plc, GlaxoSmithKline plc, and Novartis International AG for unrelated projects. M. H. has received grants-in-aid, speaker fees, and fees for serving on the advisory boards of; GlaxoSmithKline, AstraZeneca, Novartis, Teva, and Sanofi, all unrelated to the current manuscript, and all paid to his institutional employer Alfred Health. M. P. declares personal fees and nonfinancial support from AstraZeneca and GlaxoSmithKline. L. B., V. A. C., I. C., N. E., and N. H. are employees of Optimum Patient Care Global Ltd, a cofunder of the International Severe Asthma Registry. D. B. P. has board membership with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mylan, Mundipharma, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals, Thermofisher; consultancy agreements with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Novartis, Pfizer, Teva Pharmaceuticals, Theravance; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mylan, Mundipharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Respiratory Effectiveness Group, Sanofi Genzyme, Teva Pharmaceuticals, Theravance, UK National Health Service; payment for lectures/speaking engagements from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Mundipharma, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals; payment for the development of educational materials from Mundipharma, Novartis; payment for travel/accommodation/meeting expenses from AstraZeneca, Boehringer Ingelheim, Mundipharma, Mylan, Novartis, Thermofisher; funding for patient enrolment or completion of research from Novartis; stock/stock options from AKL Research and Development Ltd which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); and is peer reviewer for grant committees of the Efficacy and Mechanism Evaluation programme, and Health Technology Assessment. None declared (J. B., Y. S. C., E. S. H., R. B. M.).

The International Severe Asthma Registry (ISAR) is conducted by Optimum Patient Care Global Ltd, and cofunded by AstraZeneca plc and Optimum Patient Care Global Ltd. The ISAR steering committee comprises 43 experts in the field of severe asthma who contribute or have agreed to contribute data to ISAR. AstraZeneca plc has four members on the ISAR steering committee. All countries taking part in ISAR have one vote each when selecting the annual core global and prioritized research projects, and AstraZeneca plc has a single vote. Optimum Patient Care Global Ltd is responsible for database management and data processing and analyses and holds the casting vote in the event of ties.

Role of sponsors: OPC and AstraZeneca co-sponsor the ISAR initiative, but only members of the ISAR Steering Committee had a role in study design, collection and analysis of data and manuscript preparation.

Other contributions: The following individuals have contributed substantially to the International Severe Asthma Registry. Italy: Concetta Sirena, PhD; Severe Asthma Web-based Database: Philip Bardin, PhD, Jeff Bowden, BM, BS Li Ping Chung, MBBS (Hons), PhD, Belinda Cochrane, BMedSc, MBBS (Hons), MD, Jeffrey Garrett, MBChB, Lata Jayaram, MBChB, PhD, Christine Jenkins, AM, MD, Connie Katelaris, MBBS,

PhD, Gregory Katsoulotos, BSc(Med), MBBS (Hons), PhD, Mariko Koh Siyue, MBBS, FCCP, Vicky Kritikos, PhD, David Langton, MD, Peter Middleton, MBBS(Hons), BSc(Med), PhD, Heather Powell, MMedSci, Helen Reddel, MBBS, PhD, Paul Reynolds, MBBS, PhD, Janet Rimmer, MBBS (Hons), MD, John Upham, PhD, Peter Wark, BMed, PhD, Ian Yang, MBBS, PhD, Elaine Yap, MBChB; United States: Margo Brown, BS, Jessica Madrid, BS, Christena Kolakowski, MS, Joy Zimmer, BS.

Additional information: The e-Appendix, e-Figures, and e-Tables can be found in the Supplemental Materials section of the online article.

References

1. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43(2):343-373.
2. Global Initiative for Asthma. Difficult-to-treat & severe asthma in adolescent and adult patients: diagnosis and management—a GINA pocket guide for health professionals, V2.0 April 2019. https://ginasthma.org/wp-content/uploads/2019/04/GINA-Severe-asthma-Pocket-Guide-v2.0-wms-1.pdf. Accessed January 2, 2020.
3. Caminati M, Senna G. Uncontrolled severe asthma: starting from the unmet needs. *Curr Med Res Opin*. 2019;35(2):175-177.
4. Nordon C, Grimaldi-Bensouda L, Pribil C, et al. Clinical and economic burden of severe asthma: a French cohort study. *Respir Med*. 2018;144:42-49.
5. Gupta RP, Mukherjee M, Sheikh A, Strachan DP. Persistent variations in national asthma mortality, hospital admissions and prevalence by socioeconomic status and region in England. *Thorax*. 2018;73(8):706-712.
6. Majeed H, Moore GWK. Influence of the Scandinavian climate pattern on the UK asthma mortality: a time series and geospatial study. *BMJ Open*. 2018;8(4):e020822.
7. Sinharoy A, Mitra S, Mondal P. Socioeconomic and environmental predictors of asthma-related mortality. *J Environ Public Health*. 2018:9389570.
8. Volmer T, Effenberger T, Trautner C, Buhl R. Consequences of long-term oral corticosteroid therapy and its side-effects in severe asthma in adults: a focused review of the impact data in the literature. *Eur Respir J*. 2018;52(4):pii 1800703.
9. Foster JM, McDonald VM, Guo M, Reddel HK. "I have lost in every facet of my life": the hidden burden of severe asthma. *Eur Respir J*. 2017;50(3):pii 1700765.
10. Kerkhof M, Tran TN, Soriano JB, et al. Healthcare resource use and costs of severe, uncontrolled eosinophilic asthma in the UK general population. *Thorax*. 2018;73(2):116-124.
11. Voorham J, Xu X, Price DB, et al. Healthcare resource utilization and costs associated with incremental systemic corticosteroid exposure in asthma. *Allergy*. 2019;74(2):273-283.
12. Canonica GW, Colombo GL, Bruno GM, et al. Shadow cost of oral corticosteroids-related adverse events: a pharmacoeconomic evaluation applied to real-life data from the Severe Asthma Network in Italy (SANI) registry. *World Allergy Organ J*. 2019;12(1):100007.
13. Sadatsafavi M, Lynd L, Marra C, et al. Direct health care costs associated with asthma in British Columbia. *Can Respir J*. 2010;17(2):74-80.
14. Hansen CL, Baelum J, Skadhauge L, et al. Consequences of asthma on job absenteeism and job retention. *Scand J Public Health*. 2012;40(4):377-384.
15. Hiles SA, Harvey ES, McDonald VM, et al. Working while unwell: workplace impairment in people with severe asthma. *Clin Exp Allergy*. 2018;48(6):650-662.
16. World Health Organization. Asthma: WHO's role and activities. https://www.who.int/respiratory/asthma/activities/en/. Accessed January 2, 2020.
17. Global Asthma Network. The Global Asthma Report: 2018 update. http://www.globalasthmareport.org/Global%20Asthma%20Report%202018%20EMBARGOED.pdf. Accessed January 2, 2020.
18. Heaney LG, Brightling CE, Menzies-Gow A, Stevenson M, Niven RM. British Thoracic Society Difficult Asthma Network. Refractory asthma in the UK: cross-sectional findings from a UK multicentre registry. *Thorax*. 2010;65(9):787-794.
19. Newby C, Heaney LG, Menzies-Gow A, et al. Statistical cluster analysis of the British Thoracic Society Severe Refractory Asthma Registry: clinical outcomes and phenotype stability. *PLoS One*. 2014;9(7):e102987.
20. McDonald VM, Hiles SA, Godbout K, et al. Treatable traits can be identified in a severe asthma registry and predict future exacerbations. *Respirology*. 2019;24(1):37-47.
21. Schleich F, Brusselle G, Louis R, et al. Heterogeneity of phenotypes in severe asthmatics: the Belgian Severe Asthma Registry (BSAR). *Respir Med*. 2014;108(12):1723-1732.
22. Korn S, Hübner M, Hamelmann E, Buhl R. The German severe asthma registry [in German]. *Pneumologie*. 2012;66(6):341-344.
23. Vennera MDC, Pérez De Llano L, Bardagí S, et al. Omalizumab therapy in severe asthma: experience from the Spanish registry—some new approaches. *J Asthma*. 2012;49(4):416-422.
24. Heffler E, Blasi F, Latorre M, et al. The Severe Asthma Network in Italy: findings and perspectives. *J Allergy Clin Immunol Pract*. 2019;7(5):1462-1468.
25. Kim MH, Kim SH, Park SY, et al. Characteristics of adult severe refractory asthma in Korea analyzed from the Severe Asthma Registry. *Allergy Asthma Immunol Res*. 2019;11(1):43-54.
26. ISAR Study Group. International Severe Asthma Registry (ISAR): mission statement. *Chest*. 2020;157(4):805-814.
27. Bulathsinhala L, Eleangovan N, Heaney LG, et al. Development of the International Severe Asthma Registry (ISAR): a modified Delphi study. *J Allergy Clin Immunol Pract*. 2019;7(2). 578.e2-588.e2.
28. Global Initiative for Asthma. Global strategy for asthma management and prevention—updated 2018. https://ginasthma.org/wp-content/uploads/2018/04/wms-GINA-2018-report-V1.3-002.pdf. Accessed January 2, 2020.
29. Luskin AT, Antonova EN, Broder MS, Chang EY, Omachi TA, Ledford DK. Health care resource use and costs associated with possible side effects of high oral corticosteroid use in asthma: a claims-based analysis. *Clinicoecon Outcomes Res*. 2016;8:641-648.
30. Sullivan PW, Ghushchyan VH, Globe G, Schatz M. Oral corticosteroid exposure and adverse effects in asthmatic patients. *J Allergy Clin Immunol*. 2018;141(1):110.e7-116.e7.
31. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol*. 2004;113(1):59-65.
32. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J*. 1999;14(4):902-907.
33. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. *Eur Respir J*. 1993;6(suppl 16):5-40.
34. Lung function testing: selection of reference values and interpretative strategies—American Thoracic Society. *Am Rev Respir Dis*. 1991;144(5):1202-1218.
35. Jun-ho B. South Korea officially an aged society just 17 years after becoming aging society. *Hankyoreh*. August 28, 2018. http://english.hani.co.kr/arti/english_edition/e_national/859608.html. Accessed January 2, 2020.
36. Douwes J, Brooks C, van Dalen C, Pearce N. Importance of allergy in asthma: an epidemiologic perspective. *Curr Allergy Asthma Rep*. 2011;11(5):434-444.
37. Jung SJ, Park SH, Choi EK, et al. Beneficial effects of Korean traditional diets in hypertensive and type 2 diabetic patients. *J Med Food*. 2014;17(1):161-171.

38. Park SY, Jung H, Kim JH, et al. Longitudinal analysis to better characterize asthma-COPD overlap syndrome: findings from an adult asthma cohort in Korea (COREA). *Clin Exp Allergy*. 2019;49(5):603-614.

39. Park M, Luo S, Kwon J, et al. Effects of air pollution on asthma hospitalization rates in different age groups in metropolitan cities of Korea. *Air Qual Atmos Health*. 2013;6(3). https://doi.org/10.1007/s11869-013-0195-x. . Accessed January 2, 2020.

40. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med*. 2006;355(21):2226-2235.

41. Bleecker ER, Wechsler ME, FitzGerald JM, et al. Baseline patient factors impact on the clinical efficacy of benralizumab for severe asthma. *Eur Respir J*. 2018;52(4):pii 1800936.

42. National Institute for Health and Care Excellence. Benralizumab for treating severe eosinophilic asthma: technology appraisal guidance [TA565]. www.nice.org.uk/guidance/ta565. Accessed January 2, 2020.

43. National Institute for Health and Care Excellence. Mepolizumab for treating severe refractory eosinophilic asthma: technology appraisal guidance [TA431]. www.nice.org.uk/guidance/ta431. Accessed January 2, 2020.

44. British Thoracic Society. BTS/SIGN British guideline on the management of asthma. https://www.brit-thoracic.org.uk/quality-improvement/guidelines/asthma/. Accessed January 2, 2020.

45. Chiu KC, Boonsawat W, Cho SH, et al. Patients' beliefs and behaviors related to treatment adherence in patients with asthma requiring maintenance treatment in Asia. *J Asthma*. 2014;51(6):652-659.

46. Pavlidis S, Takahashi K, Ng Kee Kwong F, et al. "T2-high" in severe asthma related to blood eosinophil, exhaled nitric oxide and serum periostin. *Eur Respir J*. 2019;53(1):pii 1800928.

47. Fitzpatrick AM, Moore WC. Severe asthma phenotypes: how should they guide evaluation and treatment? *J Allergy Clin Immunol Pract*. 2017;5(4):901-908.

48. Jones TL, Neville DM, Chauhan AJ. Diagnosis and treatment of severe asthma: a phenotype-based approach. *Clin Med (Lond)*. 2018;18(suppl 2):s36-s40.

49. Kallieri M, Papaioannou AI, Papathanasiou E, Ntontsi P, Papiris S, Loukides S. Predictors of response to therapy with omalizumab in patients with severe allergic asthma: a real life study. *Postgrad Med*. 2017;129(6):598-604.

50. Hanania NA, Wenzel S, Rosén K, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med*. 2013;187(8):804-811.

51. Casale TB, Chipps BE, Rosén K, et al. Response to omalizumab using patient enrichment criteria from trials of novel biologics in asthma. *Allergy*. 2018;73(2):490-497.

52. Ortega HG, Yancey SW, Mayer B, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. *Lancet Respir Med*. 2016;4(7):549-556.

53. Li G, Sajobi TT, Menon BK, et al. Registry-based randomized controlled trials: what are the advantages, challenges, and areas for future research? *J Clin Epidemiol*. 2016;80:16-24.